REMARKS

Claims 1, 10, 17, 41-43 and 45-53 are pending in the present application. Independent claims 1, 10, 17 and 41 have been amended herein to require that the Pim-1 polypeptide be purified and further to clarify the identifying step. Claims 1, 10, 17, and 51-53 also have been amended to indicate that the tumors are solid tumors. Support for these amendments can be found, for example, in Applicant's specification at page 5, lines 27-29, page 6, lines 25-35, page 16, lines 6-12, and page 24, lines 6-11. No new matter has been added.

Claims 1, 10, 17, 41-43 and 45-53 are currently pending. Applicants respectfully request reconsideration of the pending claims.

Rejection Under 35 U.S.C. § 102(b)

The Examiner rejected claims 1, 10, 17, 41-43, and 45-50 under 35 U.S.C. § 102(b) as being anticipated by Wang et al. (*Arch. Biochem. & Biophys.* 390:9-18, 2001A). Specifically, the Examiner alleged that Wang et al. (2001A) actively perform steps (a), (b), and (c) of the claimed methods and, therefore, inherently perform methods of screening for therapeutic agents for cancer, apoptosis-inducing agents, and anticancer agent potentiators as recited in the present claims. The Examiner also alleged that Wang et al. disclose an anti-Pim-1 antibody and teach methods of detecting Pim-1 activity by determining the expression level of a reporter gene. Applicants respectfully traverse this rejection with respect to the pending claims.

A claim is anticipated under §102(b) only if each and every limitation is disclosed in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 639 (Fed. Cir. 1989) and MPEP §2131. As indicated herein, independent claims 1, 10, 17 and 41 have been amended to require that the Pim-1 polypeptide be purified. Wang et al. (2001A) uses cells that express Pim-1 (see, for example, Figure 5), and do not disclose using a purified Pim-1 polypeptide. In addition, Wang et al. (2001A) disclose that "the kinase activity of the Pim-1 molecule is not altered" upon treatment with PMA (see Figure 5A and discussion of Figure 5). Thus, Wang et al. (2001A) fail to identify a test substance that inhibits the phosphorylating

activity of the purified Pim-1 polypeptide, as is required by step (c) of independent claims 1, 10, 17 and 41.

In addition and contrary to the Examiner's assertion regarding dependent claims 43, 46, 48 and 50, Applicants are not claiming a method in which a 'Pim-1 antibody recognizes phosphorylated Pim-1.' Rather, pending claims 43, 46, 48, and 50 recite detecting the phosphorylation activity of the Pim-1 polypeptide "using an antibody that recognizes the phosphorylated form of the ... *substrate*" (emphasis added; see, for example, the specification at page 17, lines 18-26). Wang et al. (2001A) teach an antibody (anti-PTP-U2S) that recognizes a peptide that is known to be phosphorylated by Pim-1 (PTP-U2S) but, significantly, the antibody is not specific to the phosphorylated form of the peptide (i.e., the substrate). Therefore, Wang et al. (2001A) do not disclose the methods of claims 43, 46, 48 and 50.

Also, regarding the rejection of dependent claims 42, 45, 47, and 49, Wang et al. (2001A) do not disclose "detecting phosphorylation activity using, as an indicator, a change in the expression level of a reporter gene that is activated in response to binding of a ... Pim-1 phosphorylation substrate." Wang et al. (2001A) disclose the use of reporter constructs to monitor cell differentiation and identify cells undergoing apoptosis (see, for example, page 15 (Figure 8) and page 16 (table II) of Wang et al. (2001A)) and, contrary to the Examiner's assertion, Wang et al. (2001A) do not disclose that the phosphorylation activity of Pim-1 is detected by a change in the expression level of a reporter gene that is activated in response to binding of a Pim-1 phosphorylation *substrate*, as required by claims 42, 45, 47 and 49.

Wang et al. (2001A) do not disclose each and every element and, therefore, do not anticipate the pending claims. In view of the amendments and remarks herein, Applicants respectfully request reconsideration and withdrawal of the rejection of the pending claims under 35 U.S.C. §102(b).

Rejections Under 35 U.S.C. §103(a)

The Examiner rejected claims 1, 10, 17, 41-43, and 45-53 under 35 U.S.C. § 103(a) as being obvious over Wang et al. (2001A) in view of Wang et al. (*J. Vet. Sci.* 2:167-169, 2001B). Specifically, the Examiner asserted that it would have been *prima facie* obvious to use the methods of identifying agents, as allegedly taught by Wang et al. (2001A), for therapeutic

purposes for cancer, including pancreatic cancer, as allegedly taught by Wang et al. (2001B). Applicants respectfully traverse the Examiner's rejection.

As clarified by the Supreme Court, for an invention to be obvious under §103, analysis of the differences between the claimed subject matter and the prior art must reveal an explicit rationale for why one having ordinary skill in the art would have combined the elements in the manner claimed. *KSR International v. Teleflex Inc.*, 127 S.Crt. 1727 (2007). As stated by the Court, it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *Id.*

The claimed invention is directed toward a method of identifying test substances that inhibit Pim-1 phosphorylation activity, and the pending claims require that the test substance be contacted with purified Pim-1 polypeptide. On the other hand, Wang et al. (2001A) contacted a "test substance" with U937 leukemia cells that express Pim-1. In addition, it would be understood by those in the art that cells selectively import and export substances across the plasma membrane. In particular, an active transport system on the plasma membrane can selectively transport molecules out of cells (see, for example, Schlemmer & Sirotrak (1994, *J. Biol. Chem.*, 269(49):31059-66; see attached), which discloses that vinblastine (VBL), an antitumor vinca alkaloid, is actively transported out of vinca alkaloid-resistant erythroleukemia cells (see, e.g., page 31059, right column, line 6 to page 31060, left column, line 38)). Therefore, Wang et al. (2001A) would not have known whether or not a test substance inhibits Pim-1 activity, as the test substance might never have been able to enter the U937 cells or may have been actively transported out of the U937 cells. Thus, Wang et al. (2001A) could not have reliably identified whether or not a test compound inhibited the activity of Pim-1 and, therefore, would not have been able to identify whether a test substance was a therapeutic agent, an apoptosis-inducing agent, or an anticancer agent potentiator.

The claimed invention also is directed toward a method of identifying test substances that inhibit Pim-1 phosphorylation activity and can be used as a therapeutic agent, an apoptosis-inducing agent or an anticancer agent potentiator for solid tumors. Wang et al. (2001B), on the other hand, merely describes the relationship between the expression of Pim-1 and hematopoietic neoplasias such as lymphomas. Wang et al. (2001B) teaches that (i) hematopoietic growth factors induce Pim-1 to promote the proliferation of hematopoietic cell lines; and (ii)

overexpression of Pim-1 accelerates lymphoproliferation in transgenic mice (see, e.g., "Pim-1 and tumorigenesis" on page 168, and "Pim-1 and proliferation" on page 170). Wang et al. (2001B) neither discloses nor suggests that Pim-1 is involved in solid tumors. It would be understood by those in the art that the intracellular and extracellular environments of solid tumors differ from those of hematopoietic neoplasias (e.g., solid tumor cells can be exposed to hypoxic conditions (see, e.g., the "Background Art" on page 1 of the present specification)) and that the gene and protein expression patterns and the activities of various signal transduction pathways in solid tumors would differ from those in hematopoietic neoplasia. Wang et al. (2001B) does not contain any disclosure regarding the relationship between the expression of Pim-1 and solid tumors.

There is no disclosure in Wang et al. (2001A, 2001B, or the combination thereof) that would have prompted one of skill in the art to screen for agents that inhibit the phosphorylating activity of Pim-1 polypeptides, wherein those agents that *inhibit* the phosphorylating activity of Pim-1 can be used as therapeutic agents for cancer (independent claim 1), as apoptosis-inducing agents (independent claim 10), and as anticancer agent potentiators (independent claim 17). The relationship between Pim-1 and solid tumors is not obvious in view of the combination of Wang et al. references (2001A and 2001B) and neither reference discloses the use of a purified Pim-1 polypeptide.

For at least the reasons discussed herein, the pending claims are not obvious and are patentable over Wang et al. (2001A) in view of Wang et al. (2001B). Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of the pending claims under 35 U.S.C. §103(a).

CONCLUSION

In light of the above remarks, Applicants respectfully request that claims 1, 10, 17, 41-43 and 45-53 be allowed. The Examiner is invited to telephone the undersigned Agent if such would expedite prosecution. Please apply any charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

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